REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Applicants assert that the present invention is new, non-obvious and useful. Prompt consideration and allowance of the claims is respectfully requested.

Status of Claims

Claims 1 – 36 are pending in the application. Of the above claims 12 – 28 are withdrawn from consideration. Applicants reserve all rights in these claims to file divisional and/or continuation patent applications

Claims 1 – 11 and 29 - 36 have been rejected by the Examiner. Claims 1 and 6 are submitted as new claims. Claims 2 – 5, 7 – 9, 29 – 33 and 35-36 have been amended. Claims 1, 6, 10, 11 and 34 have been canceled. .

Applicants respectfully assert that the amendments to the claims add no new matter.

CLAIM REJECTIONS

35 U.S.C. § 112 Rejections

In the Office Action of March 17, 2008, the Examiner rejected claims 1 – 5, 11, 29-36 under 35 U.S.C. § 112, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection in view of the remarks that follow.

The Examiner states that the term "integrated viral complex" involved in the original claims 1-11 and 29-36 was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In order to meet the Examiner's rejection, the applicant depletes the term "integrated viral complex" from all the above mentioned claims and replaces it by the term "vaccine". Moreover, the term "vaccine" is **consistently** recited in the currently amended claims 1 – 11 and 29 - 36. Therefore the amended and newly submitted claims 1 - 11 and 29 - 36 now comply with the enablement requirement under 35 U.S.C. 112.

Furthermore, complying with the Examiner's rejections regarding the explicit definition of the term "integrated viral complex" in the specification, the applicant substitutes the original claim1 by a new submitted one as detailed in the aforesaid claim 1:

> ***"A live vaccine comprising a non viable dried cell having a cell membrane and a viable virion contained within said cell."***

In the new amended claim 1 the term "live vaccine" replaces the term "integrated viral complex" which was rejected by the Examiner. In the newly amended claim 1 the term "live vaccine" is defined as:

> *"...a **non-viable** **dried cell** having a **cell membrane** and a **viable virion** contained within said cell".*

For each term in the new amended claim 1, a solid basis and literal support is provided in the specification section of the original filed application (i.e. **US 2007/0111211)** in such a way as to enable one skilled in the art to make and/or use the invention, as demonstrated in the following arguments:

The phrase "live vaccine" is well described in the Description section of the specification:

*"The present invention provides, for the first time, a **live vaccine** based upon integrated viral complexes".*

Page 4 para [0068]

*"Preparation of a stabilized cell integrated **live vaccine** in which cryoprotectant added by dose to cultured cells."*

Page 6 para [0100]

With regard to the phrase "non-viable", it is disclosed in the Summary section of the specification:

*"...a plurality of intact cell membranes, each of the intact cell membranes belonging to a **non-viable** cell;"*

Page 2 para [0014]

As well as in the Description section of the specification:

*"...viable virions contained in essentially intact cell membranes of **non-viable** host cells".*

Page 2 para [0015]

The phrase "dried cell" is well described in the Summary and Description sections of the specification as provided in the following citations:

*"According to still further features in the described preferred embodiments method further includes **drying** the population of individual cells."*

Page 2 para [0027]

*"Optionally, but preferably, method 20 further includes **drying** 36 the population of individual cells. Drying may be, for example, by lyophilization."*

Page 4 para [0061]

*"In order to establish the storage characteristics of integrated viral complexes according to the present invention, the titer of experimental batches of freeze **dried cell** integrated viral complex based CVI988 vaccine was tested after acceleration of storage conditions."*

Page 7 para [0106]

*"Cell dehydration may be effectuated by several methods, e. g. freeze **drying** or vacuum **drying**."... "The vaccine bulk preparation can be filled out in vials and can be **dried** if desired by freeze **drying**."*

Page 5 para [0079]

The phrase "cell membrane" is disclosed and well defined several times in the specification section as specified in the aforesaid citations:

*"A majority of the virions of the plurality of viable virions are contained within the intact **cell membrane** belonging to the plurality of intact **cell membranes**."*

Page 2 para [0014]

*"...a plurality of viable virions, a majority of the virions of the plurality of viable virions contained within the intact **cell membrane** belonging to the plurality of intact **cell membranes**;"*

Page 2 para [0015]

With regard to the term "viable virion" in the amended claim 1, the applicant clearly described the phrase "viable virion" in the Summary section in the originally filed application specification as follows:

> *"... a plurality of **viable virions**, a majority of the virions of the plurality of **viable virions** contained within the intact cell membrane belonging to the plurality of intact cell membranes;"*

Page 2 para [0015]

It is respectfully submitted that the new amended claim 1 traverse the Examiner's rejections under 35 U.S.C 112, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Thus the applicant respectfully requests the acceptance of the amended claim 1. Claims 2 – 5 depend on new amended claim 1 and therefore meet the Examiner's objection under 35 U.S.C 112.

In view of the above arguments and citations, it is respectfully submitted that the new and amended claims 1 – 5 and 29 - 36 does not contain subject matter which was not described in the specification of the original application and thus comply with the enablement requirement under 35 U.S.C, 112. Hence, the applicant respectfully requests that claims 1 – 5 and 29 - 36 are allowable.

With regard to the independent claim 6, the applicant replaces claim 6 by a new submitted one as follows:

> *"A pharmaceutical composition comprising said **vaccine** and **stabilizing** components; wherein said components are selected from a group consisting of carriers, cryoprotectants and excipients."*

In the newly amended claim 6, the applicant uses the phrase *vaccine* which is well defined in the new submitted claim 1. Moreover, the applicant mentions the *stabilizing components* contained within the vaccine of the present invention.

The *stabilizing components* are disclosed several times in the specification of the application, namely in the description and in the examples. The *stabilizing components* mainly relate to the method of preparing the "pharmaceutical composition" of the present application. For example, the Description section discloses:

> *"The integrated viral complexes are optionally, but preferably, provided as a pharmaceutical composition for vaccination which further includes carriers,* ***stabilizers*** *and excipients."*
>
> Page 3 para [0043]
>
> *"As used herein a "pharmaceutical composition" refers to a preparation of one or more of the active ingredients described herein with other chemical components such as physiologically suitable carriers,* ***stabilizers*** *and excipients. The purpose of a pharmaceutical composition is to facilitate stability of the vaccine and administration of a compound to an organism."*
>
> Page 3 para [0044]

In view of the above mentioned arguments, the newly amended claim 6 traverse the Examiner's statement regarding the unclear basis for the claimed product. Therefore, the applicant respectfully requests that in the light of the above arguments, the herein submitted claim 6 fulfills the examiner's demands and traverses the examiner's rejection under 35 U.S.C 112.

Claim 36 has been amended so as to comply with the Examiner's objection as being confusing:

"The method according to claim 29, wherein said administering is via IM injection, subcutaneous injection or by spraying methods to chicks at 1 day of age."

Thus, in the amended claim 36, the applicant claims several alternatives for administering the vaccine to 1 day old chicks. The applicant respectfully requests that amended claim 36 is allowable.

The Examiner states that the working Example of the specification on pages 6-7 para [0100]-[0105] is confusing in many points. In order to fulfill the Examiner's objection and clarify the procedure described in the working Example, the applicant made the following amendments in the herein submitted application with regard to the following Examiners remarks:

The sentence on page 6 para [0101] line 20, relates to the previous scale-up passages, and amended to:

"The virus infected cells were harvested from the cell culture roller bottles, when 75% or more of the monolayer was cytopathically affected."

To clarify when was "the end of the incubation period", on page 6 para [0101] line 21 was amended to:

"At this point of harvest time, the whole mass of cells were washed with phosphate-buffered saline, dispersed with trypsin and resuspended in a small amount of culture medium."

Regarding the instructions for addition of Solution A in order to achieve the full range of 2-8%, the applicant accepts the Examiner's remark and corrected the mistakenly written glycerol concentration amount on page 6 para [0101] line 26 from 10% to 1%. The applicant now submits that the procedure described in the working example can be followed to achieve a full range of 2-8% glycerol and thus is not confusing.

Furthermore, the composition of Solution B is indicated on page 6 para [0102]:

> *"Solution B (stabilizer) comprising from about 0.1 to about 2% (w/v) of sodium glutamate, from about 1.0 to about 7.5% (w/v) of sucrose, from about 0.5 to about 5% (w/v) of hydrolyzed gelatin, and from about 2.0 to about 8% (v/v) of Glycerol, all in a PBS soloution in terms of the concentration in the vaccine bulk."*

In view of the above arguments and amendments, the applicant respectfully submits that the teachings in the specification of the amended application clarify what is actually contained in the clamed product. Therefore the applicant requests the allowable of claims 1-11 and 29-36.

35 U.S.C. § 103 Rejections

In the Office Action, the Examiner rejected claims 1–11, 29-34, 36 under 35 U.S.C. § 103(a), as being unpatentable over Spijkers et al, US 5789231. Applicants respectfully traverse this rejection in view of the remarks that follow.

The applicant respectfully asserts that significant modifications which are not obvious would have to be made in Spijkers and Yokogawa in order to obtain the present invention.

Spijkers teaches the preparation of vaccine by infecting quail cell line QT-35 with Marek's disease Virus of serotype 1. Spijkers claims in claim 1 the following:

> *"A method for growing Marek's Disease Virus (MDV) of serotype 1 comprising seeding the Marek's disease virus of serotype 1 onto an avian continuous cell line and incubating under conditions suitable for the reproduction of the virus on the cell line."*

In example 1 Spijkers describes the steps for the vaccine production which includes growing Marek's Disease Virus in roller bottle cultures to high titers, harvesting

the infected cell layers by trypsinzation, concentrating the cells by centrifugation, diluting the cells in freezing medium, and filling vials for frozen storage.

However, the present invention discloses, for the first time, the production of a vaccine comprising a live virion, for example Marek's Disease Virus, cocooned within a **dried cell** which contains a cell membrane, depleting from its internal content, demonstrated in the specification as follows:

> *"a plurality of **viable virions**, a majority of the virions of the plurality of viable **virions** contained within the intact **cell membrane** belonging to the plurality of intact **cell membranes**;"*
>
> Page 2 para [0015]

Therefore, the above mentioned arguments demonstrate the non obviousness of the claimed product, and respectfully traverse the Examiner's rejection under 35 USC, 103 (a).

The instant working example on pages 14-15 discloses the steps for preparation of the vaccine of the present invention as follows:

(1) Preparation of sterile stabilizer solutions A and B.

(2) Preparation of a virus infected cell suspension.

(3) Preparation of a stabilized cell integrated live vaccine in which cryoprotectant added by dose to cultured cells.

(4) distribution of the vaccine bulk to containers or vials with lyophilization.

In fact, steps (1) and (3) **were not** mentioned in example 1 of Spijkers invention nor claimed. Not only that, but also the content of Solution B is novel and disclosed on the currently amended page 6 para [0102] as follows:

> *"Solution B (stabilizer) comprising from about 0.1 to about 2% (w/v) of sodium glutamate, from about 1.0 to about 7.5% (w/v) of sucrose, from about 0.5 to about 5% (w/v) of hydrolyzed gelatin, and from about 2.0*

to about 8% (v/v) of Glycerol, all in a PBS solution in terms of the concentration in the vaccine bulk."

The purpose for using Solution B is for depleting the cell content in order to end with a host cell comprising of a cell membrane, as disclosed in the working example on page 6 para [0102]:

"The sugar(s) and cryoprotectant serve to ***osmotically deplete*** *the cytoplasmic content of the host cells while* ***leaving the host cell membrane*** *intact."*

This step of depleting the host cell cytosolic content after infecting the cells is **novel** over Spijkers, since Spijkers discloses diluting the infected cells in freezing media, without describing its exact content. The use of the freezing media in the US 5789231 is **only** for preserving the vaccine before freezing it in liquid nitrogen. While in the present invention the use of cryoprotectants and particularly Solution B is a curtail step of the preparation of the vaccine, according to Spijkers, freezing the cells in the presence of cryoprotectors such as DMSO or glycerol is **optional** and is **not** resulting in depleting the host cells cytosolic content as demonstrated in the following:

"Cells can be frozen in the presence of cryoprotectors, such as Dimethyl sulfoxide (DMSO) or glycerol. Freezing of the cells as well as the cell associated virus can be performed by establishing a gradual decrease in temperature of e.g. 1.degree. C. per minute to the desired storage temperature, which is preferably, the temperature of liquid nitrogen."

Thus, the above mentioned arguments demonstrate that the processes described in the reference example and in the working example of the present invention are not similar and hence not result in products with the same characteristics, as the examiner's states.

The applicant respectfully requests that claims 1-11, 29-24 and 36 are allowable since the claimed product seen as not obvious and contains unexpected results.

The Examiner rejected claim 35 under 35 U.S.C. 103(a) as being unpatentable over Spijkers et al US 5789231 as applied to claims 1-11, 29-34, 36 above, and further in view of Yokogawa et al, EP 1064947. The Examiner states that claim 35 differs from Spijkers in requiring vaccination in ovo; however, Yokogawa teaches vaccination of chickens in ovo with attenuated Marek's disease virus, including cell-associated virus as demonstrated in claim 1:

> *" A method for immunizing chickens which comprises inoculating into a growing egg a composition comprising either cell-free attenuated live viruses of Marek's disease type 1 or cells infected with attenuated live viruses of Marek's disease type 1 capable of producing cell-free viruses."*

Therefore, it would have been within the ordinary skill of the art to modify Spijkers by vaccination in ovo for the advantages taught in Yokogawa, with reasonable expectation of success.

Yokogawa teaches immunizing chickens with cell-free viruses or cells infected with attenuated Marek's disease virus, namely, cell-associated viruses. However the present invention discloses vaccination of ovo, comprising of viable virions contained within a host cell membrane, which is a non-viable host cell depleted from its cytosolic content, as indicated in the Abstract:

> *"Integrated viral complexes include viable virions in intact cell membranes.* ***The host cells are non-viable.***"

Thus, the method of virus preparation according to the present invention is certainly **neither** of the described virus preparation methods of Spijkers and Yokogawa, namely, cell-free or cell-associated viruses. Therefore the applicant respectfully argues that in the light of the above arguments and remarks claim 35 is not obvious over Spijkers and Yokogawa.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Respectfully submitted,

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Dated: June 16, 2008

CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

Date of Electronic Filing: June 16, 2008

I hereby certify that this correspondence is being electronically filed with the United States Patent & trademark Office on the above date.

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